FOOD AND DRUG ADMINISTRATION

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MEDICAL DEVICES ADVISORY COMMITTEE

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EAR, NOSE AND THROAT DEVICES PANEL

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MEETING

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Friday, July 21, 2000

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The panel met 9:15 a.m. in the Goshen Room of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Carl A. Patow, Chairman, presiding.

PRESENT:

CARL A. PATOW, M.D., Chairman

ALEXA CANADY, M.D., Temporary Voting Member

WILLIAM H. DUFFELL, JR., Ph.D., Industry Rep.

HOWARD FRANCIS, M.D., Temporary Voting Member

A. JULIANNA GULYA, M.D., Temporary Voting Member

LINDA J. HOOD, Ph.D., Temporary Voting Member

PRESENT (Continued):

ANJUM KAHN, M.D., Voting Member

PAUL R. KILENY, Ph.D., Voting Member

ROSS J. ROESER, Ph.D., Temporary Voting Member

CLOUGH SHELTON, M.D., Voting Member

GAYLE E. WOODSON, M.D., Voting Member

SARA M. THORNTON, Executive Secretary

FDA REPRESENTATIVES:

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TERI M. CYGNAROWICZ

I. SIDNEY JAFFEE, M.D.

JAMES K. KANE, Ph.D., CCC-A

VASANT MALSHET, Ph.D.

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SPONSOR REPRESENTATIVES (Continued):

ROBERT SHANNON, Ph.D.

STEVE STALLER, Ph.D.

CHRIS VAN DEN HONERT, Ph.D.

RONALD E. WEST, M.B.A.

PUBLIC SPEAKERS:

HENRY J. ILECKI, Ph.D.

DONNA McLAUGHLIN

GAIL UMPHREY

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(9:15 a.m.)

CHAIRMAN PATOW: I'd like to welcome you all and up front say how much I appreciate all of the hard work that the panelists have put in in reviewing the materials for today and also industry and FDA for their efforts in preparation for today.

We are very much going to try to stay on schedule, and so I will be mentioning before each speaker the time allotted for those talks so that we can keep on schedule. On the other hand, we want to make sure that we get all of the appropriate data so that we can make some good decisions.

At this time I'd like to introduce Sara Thornton, Executive Secretary, for introductory remarks.

MS. THORNTON: Good morning and welcome to the second day of the Ear, Nose, and Throat Devices Panel meeting.

Before we proceed with today's agenda, I just have a few announcements. I'd like to remind everyone that there's a sign-in sheet for attendance

record in the registration area just outside the meeting room. All handouts for today's meeting are available at the registration table.

If you have any messages for the panel members and FDA participants, information or special needs, you should direct that through Ms. Ann Marie Williams or Ms. Carol Coy, who are available in the registration area.

If you should need an assistive listening device, please see Ms. Williams or Ms. Coy.

The phone number for calls to the meeting area is (301) 948-8900.

Lunch for the panel will be in the farthest area of the restaurant. We have tables reserved back there during lunchtime for the panel and for the FDA.

In consideration of the panel, the sponsor and the agency, we ask that those of you with cell phones and pagers either turn them off or put them on vibration mode while in this room.

Lastly, will all meeting participants please speak into the microphone and give your name

clearly so that the transcriber will have an accurate recording of your comments? The panel, I believe, need do that just a few times, and then they will be clear on who is responsible for what comment.

Now, at this time before I ask the panel to introduce themselves, I'd like to extend a special welcome and introduce to the public the panel and the FDA staff, two panel consultant members who are with us for the first time today.

Dr. Howard Francis. Dr. Francis is an Assistant Professor with the Division of Neurotology and Skull Base Surgery, Department of Otolaryngology-Head and Neck Surgery at the Johns Hopkins University School of Medicine in Baltimore.

And Dr. Linda Hood is a Professor at the Kresge Hearing Research Laboratory of the South Department of Otorhinolaryngology, Louisiana State University Health Science Center in New Orleans, Louisiana.

I'd like you to know that the panel consumer representative has been prevented from attending this meeting due to illness.

I would like to extend a special welcome as I introduce to you Dr. Alexa Canady. Dr. Canady is Chief of Neurosurgery and Peter Schotanus Endowed Professor in pediatric neurosurgery at the Children's Hospital of Michigan and Vice Chairman of Neurosurgery at Wayne State University, Detroit. Dr. Canady has been a consultant on the Neurological Devices Panel of FDA's Medical Devices Advisory Committee since 1994 and currently serves as the panel chair.

Dr. Canady, we realize that your preparation and attendance was above and beyond the call of duty, and we are grateful for your willingness to participate with us today.

I'll now ask the others at the panel table to introduce themselves, starting with Dr. Duffell.

DR. DUFFELL: I'm Bill Duffell. I'm the industry rep. I am Vice President of Clinical Research and Regulatory Affairs for Cyberonics, Inc. in Houston, Texas, and beginning August 1, I'll be with Gambro BCT in a similar capacity in Lakewood, Colorado.

DR. GULYA: I am Julie Gulya, Clinical

Professor of otolaryngology, head and neck surgery at the George Washington University, and I'm also Director of the clinical trials program at the NIDCD.

DR. SHELTON: Clough Shelton. I'm a professor at University of Utah and an otologist.

DR. KAHN: I'm Angie Kahn who's in private practice in otolaryngology in Silver Spring, Maryland. I'm affiliated with George Washington University and Uniformed Services Health Sciences as Associate Clinical Professor.

CHAIRMAN PATOW: I'm Carl Patow. I'm the Executive Director for the Health Partners Institute for Medical Education. It's a large, nonprofit educational institution associated with a managed care organization in Minneapolis.

I'm also on the clinical faculty of the University of Minnesota.

DR. KILENY: I'm Paul Kileny, Professor of Otolaryngology at the University of Michigan Medical School and Director of Otology at the University of Michigan Health System.

DR. WOODSON: I'm Gayle Woodson. I'm

Professor of Otolaryngology at the University of Tennessee, Memphis, and in about a month I'll be moving to Gainesville where I'll be Professor at the University of Florida, Gainesville.

DR. ROESER: I'm Ross Roeser. I'm a Professor at the University of Texas, Dallas, in the Program and Communications Sciences and Disorders. I'm also the Director of the Callier Center for Communication Disorders, which is a component of the University of Texas, Dallas, a large center in Dallas specializing in communications disorders, and I'm a Clinical Professor at the University of Texas Southwestern Medical Center in the Department of Otorhinolaryngology-Head and Neck Surgery.

MS. BROGDON: I'm Nancy Brogdon. I'm not a member of the panel. I'm FDA's liaison to the panel. I'm the Acting Director of the Division of Ophthalmic and ENT Devices.

MS. THORNTON: Thank you very much, panel.

On behalf of the FDA, I wish to extend our sincere appreciation to the panel for the time they've taken from their busy schedules to prepare for and

participate in this meeting today.

Thank you, Dr. Patow.

I'd like to now read the conflict of interest statement for this meeting.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of impropriety. To determine if any conflict existed, the agency reviewed and submitted an agenda, and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the government.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Paul Kileny and Clough Shelton. These

panelists reported past interests in firms at issue, but in matters that are not related to today's agenda.

Therefore, the agency has determined that they may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusions will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

I'd like to read the appointment to temporary voting status for today's meeting.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27, 1990, and as amended August 18th, 1999, I appoint the following individuals as voting members of the Ear, Nose, and Throat Devices Panel for this

meeting on July 21st, 2000: Dr. Howard Francis; Dr. Julianna Gulya; Dr. Linda Hood; Dr. Ross Roeser; Dr. Alexa Canady.

For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

Signing for Dr. Feigal, Linda Kahan. Dr. Feigal is Director of the Center for Devices and Radiological Health. This is dated 7]11]2000.

Thank you, Dr. Patow.

CHAIRMAN PATOW: Thank you.

At this point, I'd like to read a charge to the panel regarding confidentiality.

I'd like to remind the panel that we're not to discuss any PMAs under consideration with anyone else, including FDA staff and other panel members. For our own protection, we must be very cautious about the perception of bias and conflict of interest that can arise at a public meeting attended

by members of industry who may be in market competition with teach other.

To that end I would caution you against having extended conversations with individuals who are not on the panel, conversations that might be misinterpreted by others as demonstrating favoritism or bias.

At this point, I'd like to go directly then to our open public hearing session. We have three individuals who have asked to speak in the open public hearing session, and I'd ask that each of them limit their comments to ten minutes or less.

The first speaker is Gail Umphrey, and I'd ask that each speaker announce, please, their affiliation and also who has paid or supported them to this conference.

Thank you.

Is Gail Umphrey here today? Yeah.

MS. UMPHREY: Okay. My name is Gail Umphrey. This is my husband, Varn.

I received the implant in 1994, and I'm very honored to be here and to be participating in the

usage of the ABI.

I just want to say -- give you some facts on what it was like before I had the implant. I had almost full hearing until about the age of 23. I was totally deaf for two years before the implant; slowly lost my hearing from 1976 to 1992.

Without hearing for the two years, I tried raising my four children, which was very difficult being totally deaf; very difficult communicating, a lot of frustration. The kids had to -- I did mainly lip reading, all lip reading. I've never had sign language training. So it would be a lot of frustration. If I couldn't understand, they would have to write a note. A lot of frustration.

So having this problem, a lot of people, including my family, friends, would leave me out of conversation because it was so difficult. That was sad for me. Like during even holidays I would find myself grabbing a magazine and going in another room and reading a magazine while my family was enjoying the holidays.

I know they didn't intend to do it, but it

was difficult. You know, very frustrated to understand on both parts.

I felt as though my family, they were taking care of me instead of I was taking care of my family. And during those two years, you know, my children just grew up more or less like without a mom. I couldn't do my part as being a full mom and wife.

I just went on day to day surviving and really not living. I would find myself if I was in a supermarket and I would see a friend, an acquaintance that I wouldn't see on a day to day basis and didn't know that I had all of these problems, I would avoid them. I would go the opposite way before they would notice me.

Now with the implant I talk to everyone, and I'm not avoiding a situation. Without the implant, during the time I was deaf, I would never ask for help from, let's say, somebody in a store or what have you. Now I do. I have no problem with that.

I have absolutely wonderful hearing with this ABI. I use the phone. I'm able to call home and check on the kids, and that was not there for two

years, of course.

Well, you can say that. Now, you know, we're able to go out with friends and continue like I did before I lost my hearing.

Can you help me? I have all of these notes sitting here.

Okay. I also was not aware of my surroundings. I think just going out and walking to the mailbox several times, and I mean my kids have even done it during the time of no hearing, the car would drive up the driveway, and of course I'd be walking up the driveway and not even be aware that there was a car behind me. Now there is no problem.

I hear birds. I hear cars and everything.

I think to sum up all of this, the two years without hearing, it was really the worst time of my life for me and also for my family. I was just surviving. That's all. In fact, at the end of the day I couldn't wait until it was bedtime so that the day was over with.

And I look back now and I wonder how I even got through the two years. It sounds scary to me

even to think of no sounds, absolutely no sound for two years.

With the NF-2, you know, NF-2 is not the greatest. It just seems to have what I have found to be able to live with it. I could deal with it. And my husband, he's by my side all through this.

Being able to hear with the ABI has given me my life back, and this is really what I would like to see for others to be able to get that sound, get their hearing back, to be able to live life to its fullest because there is so much that you miss without hearing.

I felt normal again. I felt extremely happy. There isn't anything that I do not do now. Without the ABI, I would not go to wedding functions, different entertainment functions. My family would leave, let's say, to go to a movie. I would say home because, of course, deafness; you can't hear a movie.

I go to the movie now, and I can understand that movie. So I'm part of my family.

They would do many things. They weren't intentionally leaving me out, but I would stay home in

my home. I felt safe in my home.

The ABI to me is a miracle.

CHAIRMAN PATOW: Are there any questions by the panel members?

MS. UMPHREY: The only problem with the ABI is the microphone. It's really not compatible with a microphone.

CHAIRMAN PATOW: I understand.

Just for the record, if I could ask you are you affiliated with any corporation?

MS. UMPHREY: Oh, yes. Cochlear Corporation asked me to be here only because -- and I also asked them, you know, but this had happened, and we knew it was going to happen for quite some time. I wanted them to. I wanted to be here.

CHAIRMAN PATOW: And did they pay --

MS. UMPHREY: I wanted you to hear what I had to say.

CHAIRMAN PATOW: I appreciate that.

MS. UMPHREY: Yes, they did.

CHAIRMAN PATOW: They paid your way here.

MS. UMPHREY: They paid my expenses, my

flight.

CHAIRMAN PATOW: Thank you very much.

MS. UMPHREY: Okay. Thank you.

CHAIRMAN PATOW: Thank you.

Our second speaker this morning is Donna McLaughlin.

MS. McLAUGHLIN: Do they know who I am or should I --

CHAIRMAN PATOW: If you could.

MS. McLAUGHLIN: Just checking.

Good morning.

CHAIRMAN PATOW: Good morning.

MS. McLAUGHLIN: And I bring you greetings from the great State of South Carolina. It's such an honor for me to be among such a fine group of people this morning, and I'm glad to be here.

I'm here to share with you the story of a miracle that occurred in my life last year. In 1988 I was diagnosed with neurofibromatosis 2, a genetic disorder of the nervous system. It is estimated that this conditions occurs in one in every 40,000 births and is found on genes, chromosome number 22.

In 1988, my diagnosis included bilateral acoustic neuromas. The nine tumors on both of my auditory nerves of either side of my brain stem, as well as nine other tumors in random spots between the meninges into my brain.

Since 1988 I've had three tumors removed, including two which were the acoustic neuromas, the last acoustic neuroma being removed 16 months ago. When I awoke from the long surgery, I was profoundly deaf.

In January prior to the surgery, Dr. Gary Jackson of Nashville, Tennessee informed my husband and I that I was a candidate for an auditory brain stem implant. The implant took place on March the 24th, 1999, the same day that the last tumor was removed.

I spent 60 days following the surgery in total deafness. It was such a scary and frightening time for my family and myself. In the surgery my facial nerves suffered some trauma. My taste buds suffered some shock. I've also experienced problems with depression, my equilibrium, tear ducts, saliva

glands, and swallowing.

I have learned to function, but it has been a battle every day. To some folks, they would have said that my battle would have been too much. If you can imagine, even chocolates taste bad to me.

(Laughter.)

MS. McLAUGHLIN: I've lost 65 pounds since March of '99. The weight loss within itself is a miracle.

(Laughter.)

MS. McLAUGHLIN: But not the miracle that I've come to talk to you about today. The real miracle came for me on June the 1st, 1999 when my ABI was activated. You see, I can now somewhat hear. Some folks call it the marvels of technology and some call it modern medicine. You can call it what you like. I simply call it my miracle.

My faith tells me that miracles come from God, and I believe with all my heart that I received a miracle.

Some of you may also ask what do I hear. Now that's a hard thing for me to answer, that I hear

funny things. Let me share to you.

I can hear the bell on the car when the door is left open and the keys are in it. I can hear the sound of a Kleenex being crumpled up. I can hear the wind blowing in the trees. I can hear the blinker on the car when I've left the turn signal on too long. I can hear the frogs croaking in our pond. I can hear the crickets chirping on a still night, and I can hear my dogs barking.

These are just a few of the things I hear, and they don't sound exactly like they once sounded like, but I'm hearing something, and my braining is learning exactly what I'm hearing when I hear it.

I'm still in the process of learning. The most humorous experiences happened with my ABI, and I think it does us all good to look at our life experiences and get a little laugh every now and then. So I'm going to share with you this little experience that I had.

After I got hooked up for the first time with my ABI, my hubby and I ventured down the street in Nashville, Tennessee for lunch. I went in to eat

lunch, and I went into the ladies room to wash my hands, and I washed my hands, and I tore off a paper towel, and the paper two went "zip."

Well, I stood there, and I thought, "Hey, I don't remember when I've ever heard a paper towel being torn off," or if I ever had heard a paper towel, what the sound was like. So I tore off another one.

(Laughter.)

MS. McLAUGHLIN: I sat there, and I kind of got tickled at myself, and I thought, "What are you doing?"

And in walks this lady, and she looked at me like, "What are you doing, lady?" And I could vision myself standing in a huge pile of paper towels just standing there listening to the zip.

So I began to get teary eyed and think about how blessed this little device was really going to make my life in the years to come, and I didn't tear off anymore paper towels. I just went back to eat my lunch.

I got ahead of myself. Excuse me. As the lunch has gone by, I've had numerous tune-ups, as my

children affectionately call them, at the Wilkerson Center in Nashville, and this is where I go to the audiologist, Susan Amberg, there, and she works with me patiently for hours at a time, and makes adjustments to the tones and volumes of my device.

At my first reading without the aid of my ABI, I could comprehend the lip reading only 55 percent of the time. Now, with the aid of my device and my lip reading skills, I am able to comprehend 99 percent of the time.

Today I look at life totally different. My friends tell me my self-esteem has improved immensely. I look for the blessings in my life, and I'm here to tell you that my ABI has truly been a blessing.

Since my surgery I have been blessed with many wonderful things. Let me share with you a few of them. I was blessed with the ability to hear the crowds' applause when my son, Sam Roland, won his first Tennessee walking horse national celebration down in Shelbyville, Tennessee back in September.

I was able to attend my eldest daughter's

wedding in November and know when she and my new son-in-law said, "I do."

I'm able to hear every afternoon my middle child Celia's dog bark and let me know that she's home from work.

I have been blessed with the ability to sit in church on some Sunday mornings and look at my husband and say, "I believe they're singing 'The Old Rugged Cross,' right?"

I'm really blessed. My hope is that God will grant me the resolve to use my talents and my gift of hearing to the benefit of others. Until my activation I knew no one involved in the National Ear Foundation, the Cochlear Corporation, or any of the panels -- any of the members of this panel with the Food and Drug Administration. I have no knowledge of any one of you knowing either me or my family.

However, in some wonderful way I think the Lord has brought us all together. He has allowed me to hear again, and you are a natural part of my miracle, and I thank you from the bottom of my heart.

CHAIRMAN PATOW: I want to thank you for

your comments this morning. What I need to know from you is two things. Are you affiliated with any company? And has anyone paid your way to come here today?

MS. McLAUGHLIN: Thank you.

MR. WEST: Can I help you? He needs to know if we paid your way here today, Cochlear Corporation.

MS. McLAUGHLIN: Not that I'm aware of. You invited me.

(Laughter.)

MS. McLAUGHLIN: I don't know that you did.

MR. WEST: Well, I think we did take care of her air fare.

CHAIRMAN PATOW: Thank you very much.

And thank you for your comments.

MS. McLAUGHLIN: Thank you very much.

CHAIRMAN PATOW: Our third speaker this morning is Henry Ilecki, Ph.D.

DR. ILECKI: My name is Henry Ilecki. I am the Director for Audiology Practice in Industry and

Private Practice at the American Speech-Language-Hearing Association, ASHA.

ASHA has supported or is supporting my appearance here this morning, and I have no other company affiliations.

Members of the Ear, Nose, and Throat Devices Panel, good morning, and thank you for the opportunity to offer general commentary on the use of auditory brain stem implants and the management of patients with profound hearing loss secondary to bilateral surgical lesions of the acoustic nerve.

The American Speech-Language-Hearing Association is a professional and scientific organization that represents over 98,000 audiologists, speech-language pathologists, and hearing and speech scientists. The association encourages the development, evaluation, and implementation of procedures, programs, and technologies holding promise in the areas of identification, evaluation, and treatment of individuals with hearing loss and related disorders.

The work of the Food and Drug

Administration in this regard has been highly constructive and beneficial to the public health, and there is every anticipation that results of this record will be extended into the newly expanding realm of auditory brain stem implants.

Following the diagnosis of acoustic neuromas, patient management decisions are made that are based on a variety of factors. These include the size of the tumors, the overall health of the patient, and the feasibility of hearing preservation.

When a decision is made to proceed with a surgical approach that will result in complete deafness, the only means to provide the patient with hearing postoperatively is by means of the auditory brain stem implant, or ABI.

While clinical experience with this technology is relatively limited compared, for example, to the research findings of experiences of Cochlear implantees, preliminary indications suggest that ABI recipients generally receive benefits of sound detection and discrimination that are similar to those afforded by the first generation of Cochlear

implants.

ASHA applauds this technology and recognizes the hope it provides to persons having to undergo the hearing debilitating effects of some of the surgical remedies to excise acoustic neuromas. In this promising and emerging technology, ASHA recommends the following areas of investigation be included during the FDA's deliberative process.

In reviewing desired outcomes, the question should be posed as to what extent ABIs alter recipients' perception of disability and their sense of quality of life. What differences, if any, are there between recipients of ABIs and individuals choosing not to have the procedure or different procedures? How do ABI recipients fare compared to Cochlear implant recipients?

The second broad area of study recommended by ASHA concerns the vast array of existing assistive technologies in the marketplace available to the myriad users of conventional hearing aid devices.

Assistive listening devices range in size and cost from the simple strap mounted, battery

operated telephone amplifier, to FM or infrared devices used to enhance the signal to noise ratio of stage material broadcast, to compatibly equipped hearing aid users in the audiences of concert and lecture halls.

The extent to which ABI utilizes existing assistive technology in special listening circumstances needs to be documented and, where lacking, development encouraged.

A particular concern to this clinical population, that is, persons who are bilaterally deafened, is their post implantation access to assistive technology of the alerting variety. It is essential that implantees be able to benefit from such potential life saving devices as smoke, fire, and carbon monoxide detectors and security alarms, as well as convenience announcement devices interfacing with doorbells or knockers, sleep alarms, et cetera.

ASHA urges the panel to consider a general recommendation recognizing the essential role performed by the audiologist as a critical hearing care professional in candidacy consideration and the

rehabilitative process.

Decisions relevant to the implantation process should relate to auditory status and auditory processing information derived through comprehensive pre, peri, and post implantation audiological evaluation performed by an audiologist.

Consider that even when the surgery spares the cochlear nerve anatomically, it is frequently compromised physiologically. Thus, an intact nerve following tumor excision may be unresponsive. Audiological intraoperative monitoring incorporating the auditory brain stem response should, therefore, be an essential aid to the implantation decision.

Certainly in the area of Cochlear implants, but as well in all device based forms of intervention, the critical component to successful patient outcome has been shown to be dependent upon regular intensive and quality post surgical device orientation, counseling, and rehabilitation by the audiologist. Thus, crucial areas of audiologists' participation in an ABI practice protocol would include determination of candidacy, preoperative

counseling, and post operative mapping, and otologic rehabilitation.

In addition, speech-language pathologists may also be involved in speech and voice assessment and treatment of ABI patients in need of such services.

In concluding, the review and regulation of medical devices for safety and efficacy, such as hearing aids and implantable devices, is a critically important function of the Food and Drug Administration. It is the view of the American Speech-Language-Hearing Association that in evaluating emerging technologies and applications, the Food and Drug Administration recognizes and promotes the value of an audiological component to insure the eventual clinical acceptance, utility, and successful outcomes with auditor brain stem implants.

Thank you for the opportunity of addressing this panel.

CHAIRMAN PATOW: Thank you.

I want to thank each of our speakers this morning for their valuable comments, and I'm certain

that the information they've shared will be very helpful to the panel.

At this point, we'll proceed to our open committee discussion session. Nancy Brogdon will at this time give the Division update.

MS. BROGDON: Good morning. I have several announcements to make. Most of these I said yesterday, but we have new people here on the panel and in the audience today.

First, I'd like to let you know that Dr. Ralph Rosenthal, who is our Division Director in the Division of Ophthalmic and ENT Devices, is working temporarily in our Center Director's office on Health Care Financing Administration issues. He's expected back in a few months, but I'm the Deputy Director, and that's why I'm sitting here today.

Secondly, I'd like to announce that our Office Director has been selected -- this Office Director is over the six reviewing divisions who review the whole spectrum of medical devices, and this new Director is Dr. Bernard Statland.

He was here yesterday visiting, but was

unable to be here today.

Dr. Statland received his M.D. degree and his Ph.D. in biochemistry from the University of Minnesota. He did residencies at the University of Copenhagen and the University of Minnesota Hospitals.

He also served in the Public Health Service in New Orleans and at the NIH Clinical Center.

Dr. Statland is a clinical pathologist, and he's held a number of positions, including Medical Director and CEO of laboratories at the North Shore Long Island Jewish Health System, and he has run his own consulting firm in Minneapolis. He has many publications in several areas of interest, and we're happy to have him on board.

I'd also like to announce that Mr. Harry Sauberman, who is the Chief of the ENT Branch, is working currently in the Office of Device Evaluation on special projects. Among those is partnering with governments of other countries.

In the meantime, Dr. Morris Waxler is the Acting Chief of the ENT Branch. Dr. Waxler's experience as a Branch Chief and as a

neuropsychologist made him well suited for selection to be Acting Director of this branch.

I'd like to introduce a new reviewer in the ENT Branch, Dr. James Kane. Dr. Kane is an audiologist. He has a B.S. in speech and hearing science from California University of Pennsylvania. He has his Master's and Ph.D. in audiology from the University of Pittsburgh, and he did a post doc. at the University of Pittsburgh Medical School.

He's practiced for 22 years both privately and in the Veterans Administration, and he's held various supervisory positions. Jim is a Fellow of the American Academy of Audiology, and we welcome him to the branch.

One last item. As I mentioned yesterday, we have three voting members from this panel who will have completed their four-year terms in October and probably are not likely to attend another meeting as a voting member, and presented certificates to Drs. Woodson and Duffell yesterday.

Today I'd like to read a letter from Commissioner Jane Henney, Commissioner of Food and

Drugs, to Dr. Shelton.

"Dear Dr. Shelton:

"I would like to express my deepest appreciation for your efforts and guidance during your term as a member of the Ear, Nose, and Throat Devices Panel of the Medical Devices Advisory Committee. The success of this committee's work reinforces our conviction that responsible regulation of consumer products depends greatly on the participation and advice of the nongovernmental health community.

"In recognition of your distinguished service to the Food and Drug Administration, I am pleased to present you with a certificate."

Signed Dr. Jane Henney.

That completes my announcements.

CHAIRMAN PATOW: Thank you.

I also would like to express my appreciation to each of the members who have completed their term for the hard work that they've put in in reviewing the PMAs and other documents, and in participating in these panels.

At this time we'll have the branch update.

Morris Waxler, Ph.D., will present.

DR. WAXLER: Good morning again. I'd like to introduce our branch. Our branch is Karen Baker, who's an R.N., scientific reviewer; Teri Cygnarowicz, who is an audiologist; Dr. Sid Jaffee, Sidney Jaffee, who's our Medical Officer; Dr. James Kane, our audiologist, whom you've already met; Dr. Vasant Malshet, who's our toxicologist; and Dr. Alfred Montgomery, who is not here.

(Laughter.)

DR. WAXLER: He was here just a moment. He slipped out on me.

In addition, we have reviews often from other folks at CDHR, including Dr. Brian Beard and Dr. Bill Regnault and Dr. Victor Krauthammer. I won't give the list of all of those who have helped us, but in this particular case, I would like to acknowledge Dr. Rhonda Ballum (phonetic) from the Office of Orphan Product Development. I think I got that right, and for her special role in this application.

The Cochlear Corporation received a grant from the Orphan Products Division to study this area,

and we appreciate your efforts.

That's it for me.

CHAIRMAN PATOW: Thank you, Dr. Waxler.

We'll begin now our consideration of PMA P000015, the nucleus auditory brain stem implant, presented by Cochlear Corporation.

I understand that there are seven presenters scheduled. We will have an hour for their presentation, and we will plan to end, therefore, a couple of minutes after 11 o'clock.

MR. WEST: My name is Ron West, and I'm President of Cochlear Corporation, the sponsor of PMA 000015, and this morning I'm going to give you just some context of the history of the development of this auditory brain stem device and introduce our speakers.

We do have seven speakers. Mine will be brief, and we should be able to finish on time.

The history of the auditory brain stem implant project really goes back over 20 years, and the first auditory brain stem implant was performed by Dr. William House and Dr. William Hitselberger in 1979. It was a single channel device with a ball type

electrode and was successful, and that patient is still benefitting from that implantation today.

Some five or six years later, the House Institute applied for an IDE with the ENT Branch, and that was granted, and they implanted a series of 25 patients, again, with a single channel device that utilized a platinum plate electrode.

The early cases were percutaneous connection, and it was later changed to a transcutaneous connection.

Next slide, please.

Then in the early '90s, there was a collaboration that began between Cochlear Corporation and our design people in Sydney, Australia, the Huntington Medical Research Institute, and the House Ear Institute to develop a multi-channel device. An initial series of three patients were implanted at the House Ear Institute during that period of '92 to '93, and then we filed for an IDE to expand that program in 1994.

That multi-channel device was based on the nucleus 22 stimulator design and utilized an eight

platinum disk array. That program led over the intervening seven to eight years to a premarket approval application that was filed in March, and that application is based on the nucleus 24 auditory brain stem implant and involves some 90 subjects studied for safety and 60 subjects studied for effectiveness.

That's a very brief overview of what's been a long journey to this day, and I'd like to take a moment just to thank the ENT Branch for their efforts and review of this PMA application, as well as the panel.

I know what it takes to write one of these applications, and I think it's equally or maybe more onerous to review them. They're massive in nature, and I applaud your efforts.

I would also like to acknowledge the Orphan Device Office's support of this program. Dr. Waxler mentioned that, but I think it's important that everyone understand that we might not be here today without their support.

There were actually two grants. The initial one was to the House Ear Institute and

involved, I think, $300,000 over three years, and then there was a second grant to Cochlear Corporation of a similar amount. So without that investment, I don't know that this PMA would have been possible.

So thank you, Rhonda. We really appreciate that support.

Now, if I may -- next slide, please -- I'd like to introduce our speakers.

Ms. Patti Arndt, who's our Manager of Clinical Studies, will give an overview of the PMA.

And then Professor Martyn Hyde, who is our statistical consultant and is Professor of Biostatistics at the University of Toronto, will cover the statistical design.

And then Dr. Brackmann and Dr. William Hitselberger, surgical consultants to Cochlear from the House Ear Institute, will cover device safety in surgery.

And then Ms. Kiara Ebinger, a senior clinical study specialist for Kochlear will cover the device effectiveness data.

And then we'll round out the session with

Ms. Arndt again covering the proposed labeling, post market surveillance recommendations, and conclusion.

So without further ado, I'd like to ask Patti to come up and give the overview.

MS. ARNDT: Thank you very much.

Just wait a second for the slide here.

What I'd like to do is just to describe the device that you'll be discussing and deliberating this morning and explain to you some of the bases for our recent PMA submission.

The device, as you know, is the nucleus 24 auditory brain stem implant. The N24 ABI is intended for use in individuals who are 12 years of age or older who have been diagnosed with neurofibromatosis Type 2. That's hard to say this early in the morning.

The device is implanted during the recipient's first or second side tumor removal surgery.

Next slide, please.

Just to give you a reminder, NF2 has a number of auditory manifestations. Certainly the primary symptom is the presence of bilateral

vestibular schwannomas. These tumors generally grow progressively over time, and individuals lose their hearing at the same time. So NF2 recipients demonstrate a progressive hearing loss as their tumors grow.

By the time that their second tumor is removed surgically, they are totally bilaterally profoundly deaf. Because the connection between the cochlea and the first brain stem nucleus, first auditory brain stem nucleus is disrupted, these patients aren't viable candidates for either hearing aids or cochlear implants as treatments. Really their only possible treatment, their only access to sound is through electrical stimulation of the cochlear nucleus via the ABI.

Next slide.

So the device that we're asking you to consider this morning is composed of a number of pieces. It is a system for patient use. The primary piece of this system is the implanted portion, the nucleus 24 auditory brain stem implant, which consists of a receiver stimulator and a 21 electrode brain stem

array.

The external equipment worn by the patient includes the SPrint body worn speech processor and headset. The SPrint is programmed to implement the spectral peak or SPEAK encoding strategy. Part of the headset is an adhesive retainer disk which allows patients to wear their headsets following the removal of the internal magnet from the device, which allows them ultimately to have MRIs, which are an important diagnostic tool in this population.

There are a family of speech processor accessories which allow these patients access to assistive listening devices, as was mentioned by the ASHA representative earlier.

And then lastly there are device programming systems, both a portable system, a desktop system, and some software that allow audiologists to program the devices.

As you can see from the stars on the slide, all but two of these components have been previously approved by FDA or cleared for commercial use as part of the nucleus 24 Cochlear implant system.

Next slide, please.

Just to remind you, the nucleus 24 receiver stimulator component is identical to the receiver stimulator used in the nucleus 24 Cochlear implant, which was released by FDA in June of 1998.

This particular receiver stimulator allows for some flexibility in programming options for these patients. The electronics have a capacity for high rate stimulation. The implant is capable of implementing multiple speech processing strategies. It can be programmed to implement a number of stimulation modes, three monopolar modes, a variable bipolar mode, and a common ground mode.

As I mentioned before, the magnet that is placed kind of in the center of the receiver coil can be removed for MRI, and then lastly, this particular technology allows for some comprehensive telemetry, which allows the audiologist to verify the functionality of the device and includes a tool called neural response telemetry.

Next slide, please.

This is just a picture of the device.

You've probably all seen it in a lot of detail. I'll just point out to you the magnet in the middle of the receiver coil on the right-hand side of the slide, and that generally is removed for these patients prior to implantation, which, again, allows them to undergo MRIs.

Next slide.

This is a little more detail on the brain stem electrode array. It features 21 platinum disk electrodes, each seven millimeters in diameter. The electrodes are carried or organized in a three-by-seven matrix and are carried on a silicone pad, which is eight and a half by three millimeters.

And then lastly, the electrode is backed by a T-shaped piece of mesh, and what the mesh does is it allows connected tissue to grow through the mesh following implantation, which ultimately fixes the electrode pad against the cochlear nucleus.

Next slide.

So what is the basis of our request today?

As you know, we have submitted U.S. clinical trial data collected under IDE G930077 using

the nucleus 22 auditory brain stem system. This is a system that uses the same receiver stimulator component as the commercially available nucleus 22 Cochlear implant, which is our previous generation Cochlear implant system, and it features an eight channel brain stem electrode.

We have also submitted safety and effectiveness data that was obtained as part of a European clinical trial on 27 subjects, and this receiver-stimulator component, again, is the nucleus 22 component, but this time it's coupled with a 20 or 21 channel brain stem electrode.

As Ron mentioned, the numbers in the U.S. trial are rather large. We've studied 90 subjects for safety and 60 for effectiveness.

Next slide.

In addition, we've submitted to FDA quite extensive laboratory testing, which verifies the function of the nucleus 24 ABI.

And then lastly we have clinically validated all of the components of the N24 implant. So the receiver-stimulator component, which has been

surgically implanted in over 10,000 Cochlear implantations worldwide, and then finally the 21 electrode array was evaluated as I just mentioned in Europe and has now received the European CE Mark.

Next slide.

All of that is summarized in this difficult to see slide, but the point of it is that the nucleus 24 ABI, which is described in the lower bottom right-hand box, has evolved from two different Cochlear implant systems, a previous generation system, our current system, and two different versions of an ABI system, both of which have been based on the nucleus 22 technology, one with an eight electrode array, and the other with a 20 or 21 electrode array.

Next slide.

So why are we in such an unusual situation?

I think we need to kind of recall the context that NF2 puts us in when we start studying ABIs. NF2 is a disease that occurs at a very low incidence and low prevalence. There just aren't a lot of people around to receive ABIs and to study it. In

this day and age our Cochlear implant and ABI technology is rapidly changing. We really are making very exciting improvements all the time.

So in that context, it's very hard to recruit enough investigational subjects to continually evaluate new technology.

Why do we think it's important that you approve the nucleus 24?

First of all, it's our desire to provide these patients with the current generation technology. This technology has features that are very well suited to ABI recipients and needed by them. Perhaps even more than our Cochlear implant recipients, ABI patients can benefit from the capacity of the N24 technology, its increased flexibility for programming, and ultimately its upgradability.

And then lastly, we strongly believe that we have shown the safety and effectiveness of the nucleus 24 receiver, the 21 electrode array, and certainly the SPEAK encoding strategy through the other mechanisms that I've just mentioned.

Thank you.

DR. HYDE: Good morning. I'm Martyn Hyde. I'm someone who has no financial interest in the company or in the outcome of today's proceedings, but I am being reimbursed for expenses incurred in attending this meeting.

I'd like to give you a brief, very brief outline of the experimental design and statistical methods.

Next slide, please.

I'm going to touch upon these points.

Sorry. Can you go back one.

The study design itself; the disposition of the study cohort; the analytical approach; some issues of power and sample size; and a few simple conclusions.

Next slide.

The study design was a familiar one to you, I believe, the single subject, repeated measures design replicated in 60 subjects. The key features of this design, of course, are that old treatment conditions can apply on each subject. So we can make within subject comparisons.

Most importantly about that, we can make within subject significance tests. We can do statistical significance tests within individuals using the binomial distribution, and then we achieve generalizability of those single subject results using group aggregate statistics.

Next slide.

The disposition of the cohort is summarized here. Ninety-two subjects within F2 received the implant, and two of those subjects deceased for reasons unrelated to the ABI. That leaves 90 subjects who yielded the safety data. There was a subgroup of 13 subjects who had no auditory precept on initial activation, and 17 subjects, other subjects, yielded no data.

There was a variety of reasons for that, the most common reason being that the subjects were too ill to attend the follow-up sessions.

This leaves an effectiveness cohort of 60 subjects providing effectiveness data, and these were obtained at eight sites, but I should remark that there was an overwhelming preponderance of subjects,

a substantial number of subjects at one site, more than half of the subjects.

Next slide, please.

The general analytical approach is that the subjects who lacked auditory precepts constitute a distinct and separate sub-cohort. They are qualitatively distinct from the balance of the effectiveness cohort. So they are separated and described.

The second point, the missing data, they appear in my opinion to be unrelated to probable outcome, and so I believe that there is no necessity for adjusting the outcome data for bias.

I believe, therefore, that the effectiveness cohort of 60 should be considered to be representative of the target population, and in that cohort we used completely standard descriptive or inferential statistical methods to detect and quantify the treatment effects.

Next slide, please.

We targeted outcome data at six months, but some subjects did not have six month data

available at the time of analysis. They offered three month data. Therefore, we believe that because it's possible that they might not have achieved the asymptotic performance levels at six months, this outcome data may be slightly conservative.

The actual outcome measures were various and may be divided into four main areas: the sound and speech recognition test; the test of lip reading enhancement; and two secondary measures, which are subjective performance ratings and subjective benefit ratings.

Next slide, please.

The specific statistical methods that we used, we used single subject significance tests of improvement from chart score for the sound recognition tests. These tests are, of course, one-tailed because you can't get worse than chance score, and they were based on the binomial model.

The second thing, we used single subject significance tests if performance changed with device activation and without device activation. These tests are conservatively two-tailed, and of course, based on

the binomial distribution as well.

We summarized the cohort data by using proportions of subjects who had statistically significant improvements or achieved specific performance levels. I just want to point out that that is, in fact, an extremely conservative approach. It is unusual to have statistical significance in an individual, and simply to count the proportion of people who achieved that is a conservative representation of the outcome.

And then we used other statistics that are always required by FDA in these kinds of designs, typical ones such as just group means, medians, and standard deviations.

Next slide, please.

A few comments on power. Power, of course, as you all know, is the probability of detecting a treatment effect when it genuinely exists, and we usually need to prove that we can achieve a power level of .8, .9, with an alpha of less than .05.

Group size is usually computed to achieve the target power for a minimum practically significant

treatment effect size.

In this single subject design, the significance tests are possible in individuals. So the single subject power is dictated mainly by the number of items in the test list. That's the basic feature of the binomial model, and the power depends purely on the number of items in the test list.

But we also require high group power in order to confirm the consistency of effects across subjects and to imply that the findings are generalizable.

Next slide, please.

What we found was highly significant improvements for several of the primary measures and in many individual subjects. For several of the primary measures the actual group power that we found was extremely high, such that the likelihood of the observed results being obtained by chance if there were no treatment effects is close to zero, virtually negligible, massive statistical significance at the group level.

So I believe that the power of the

experiment was clearly sufficient at both the single subject and the group levels. The cohort sample size and effect consistency were also, I believe, sufficient to yield reasonable generalizability of the findings.

So my simple conclusions, in my opinion, the study sample is representative and is sufficient. the statistical approach and methods used were valid and were appropriate, and the proposed performance claims are conservative and are fully supported by the data.

Thank you.

DR. BRACKMANN: Hello. I'm Derald Brackmann. I'm an otologist, neurotologist, and practice at the House Ear Clinic in Los Angeles. I am on the Medical Advisory Board of Cochlear Corporation. They have paid my expenses to this meeting. I have no financial interest in the company other than that.

Safety of a device, of course, is of utmost importance. By our oath we are committed to do no harm, and I know that is the FDA's primary concern as well, that devices must prove to be safe as well as

effective.

But safety is of paramount importance. I'd like to address that.

Next slide, please, Jennifer.

The quick review -- I know this is redundant for most of you. You've already heard that the external receiver stimulator is identical to the currently used Cochlear implant devices.

Cochlear implants, of course, are not appropriate for patients with NF2 because in most cases in removal of their tumor the auditory never, the pathway to the higher centers, is destroyed. So you may think of this as just like a Cochlear implant, except that the interface with the auditory pathway is at the next substation or next way station, the cochlear nucleus.

So it's identical in many ways except that the electrode stimulates the next higher pathway in the auditory chain.

Next, please.

Fortunately, nature was kind to patients and to us in that the cochlear nucleus lies on the

roof of a natural pathway from the brain stem. It lies in the roof of the lateral recess of the fourth ventricle. So the electrode can be placed onto the surface of the cochlear nucleus without the necessity of putting anything into the brain itself.

So there's a natural pathway which will hold the electrode in position, and the electrode is designed to fit exactly into that natural pathway so that upon insertion, it will be in surface contact with the cochlear nucleus and thus stimulate the auditory pathway.

Next, please.

So this is obviously not a real tumor, but a simulation of a tumor that shows the lateral recess of the fourth ventricle. The flocculus lies posteriorly, and you locate the eighth nerve, follow the eighth nerve into the lateral recess and then insert the electrode over the surface of the cochlear nucleus in the lateral recess of the fourth ventricle.

And as I said, the electrode is designed to fit in that it has a carrier of dacron which has some surface adhesion, which will hold the electrode

in place.

Next please.

The total number of patients that have been implanted is 92. Two succumbed to the disease prior to stimulation, and so that we have safety data on the remaining 90 subjects.

I do want to spend a minute telling about those two patients because those, of course, that's the ultimate complication, and I do want to address that briefly.

One patient died of serratia meningitis. This is a Gram-negative meningitis. He had done very well in surgery. In fact, he was discharged from the hospital, seemed to be doing well. He developed a headache, was readmitted, and initially had negative spinal fluid cultures.

In infection was being harbored in the ventricle, in the lateral ventricle. He then had a sudden turn for the worst and positive cultures for serratia. Serratia meningitis has an overall mortality of about 80 percent. It's extremely virulent, extremely difficult to treat. We had a

limited autopsy. There was no evidence of infection or loculation of any pus or infection around the implant. We do not believe that his death or his meningitis and death was in any way related to the auditory brain stem implant.

The other death was a patient who had an early massive tumor. He had an early stroke, a brain stem stroke, never recovered from that. He never gained consciousness so he could be stimulated. Again, there was no evidence of any relationship to the auditory brain stem implant.

So we believe that these two deaths were related to disease and not to the auditory brain stem implant.

Next slide, please.

Complications for the remaining 90 patients we divided into three groups. As you see here, minor complications were those that could be resolved by either changing the external device. Some of them just resolved spontaneously. Some required reprogramming, things of that nature. All of the minor complications were resolved with these measures.

Major complications were those that required hospitalization, revision or removal of the implant.

And finally, a complication -- it could be called a complication, but as I'll show you in a minute, there were a number of patients who did not receive auditory precepts from the device, and they did not require removal or any treatment, but they did not benefit from the device because they did not stimulate.

Next slide, please.

First I'll address the non-stimulation patients. There's a little confusion in the data because there are actually 14 who did not stimulate at first hook-up, and there's 13 that you see at the top of this graph, and then there's non-stimulation with the first ABI, who subsequently performed well with the second ABI. So if you take those two groups, there were 14 who did not stimulate at initial hook-up.

Two patients had good stimulation for a period of time, in one case a couple of years, and

then had deterioration of the device. In these cases, in one of them, CT identified that the electrode had migrated, and the other the cause was unknown, but there was non-stimulation initially on 14 of the patients.

Next, please.

Two major complications. In one case the skin broke down over the receiver stimulator. A flap was placed over this, but that flap also broke down, and the patient had poor skin turgor. It was deemed that it was not reasonable to continue to try to cover it, and the patient elected and the physicians concurred that it was best to remove the device.

The electrode was cut in the mastoid cavity. The electrode pad was not removed from the brain stem. There have been no further complications. The skin healed, and there have been no further complications related to that.

Another patient developed a skin flap infection. A decision was made to revise the flap. During the revision, the electrode was moved, and intraoperatively electrically evoked response.

Audiometry responses could not be obtained, and it was again elected to remove the device, and the skin healed and there have been no further sequelae, but the patient, of course, has no benefit from the device.

All of the other complications that are listed there are minor and temporary. At the time of initial stimulation, one patient had fluid beneath the flap which subsequently resolved. One patient had some dizziness, and one electrode was found to produce that. That electrode was programmed out of the device, and that was resolved.

The headache resolved spontaneously, and deprogramming two electrodes resulted in relief of the light headedness/dizziness with the device use.

So all of these complications, except the two that required explanation, have been resolved either expectantly or with device reprogramming.

Next, please.

Some considered device complications. You know, the magnets are removed, and nobody has yet mentioned, but this is compatible with MRI. We have

done hundreds of MRIs on these patients. So there's no internal ferromagnetic material.

The way the device is held in place is that the patients glue a metallic disk over the implant, and two patients have had some irritation from the glue. One has solved that by using adhesive on either side of the disk. The other just by changing it every night, not leaving it on for three or four days the way some patients do. So that problem has been resolved.

Two patients had some sound quality changes, one after a surgery for the other side, and that was reprogrammed, and the problem resolved.

One patient heard some clicking and popping, and we offered to reprogram it, and he said, no, it went away, and there was one patient who had pain on electrode, one electrode or two electrodes actually, and they were programmed out and that problem solved.

So next slide, please.

So when you address, again, going back, addressing the initial question that I posed, is it

safe. We believe it is. The extrusion rate is very similar to Cochlear implants. That's a known complication of Cochlear implants. The flaps need to be designed well, but no problems, no harm was done except that the patient doesn't hear after explanation of the device.

Next, please.

All but two of the medical surgical complications were minor. They were all resolved with reprogramming or with doing something with the device of a minor nature. The non-stimulators are a problem that is apparent.

Next, please.

The European data supports our experience. In Europe, there have been on ABI related neurological problems reported. They have not had major complications attributed to the ABI, and so their experience has been similar to ours.

Next, please.

So to summarize, I think these things have already been said. Seventeen, point, eight percent of the subjects do not receive auditory precepts. In the

majority of those, it's distortion of the cochlear nucleus at the time of surgery. These patients in our series in the United States, two-thirds of the patients were done at the time of second tumor removal. These patients typically hold onto their hearing and tumors as long as possible.

These are huge tumors by the time the second tumor is removed, and there's distortion in the area of the brain stem and cochlear nucleus which makes device placement difficult in some cases.

The other complications are minor and have been resolved with reprogramming. There have been no life threatening complications or risks that we have been able to associate with the auditory brain stem implant. There have been no device failures over an eight-year period.

So I conclude that the device is safe and that no patient has been harmed by its placement.

Thank you.

DR. HITSELBERGER: I'm Dr. Hitselberger, and I don't have any business connections with Cochlear or anybody else.

(Laughter.)

DR. HITSELBERGER: They paid for my way to come here.

I'm going to talk about the neurologic evaluation. Most of this stuff, I think, you all know. One in 40,000, I just computed that. That means that there are 6,250 patients in the United States with NF2. Whether they all come to have an implant I don't know.

Bilateral eighth nerve tumors, and the symptoms from these tumors vary depending on the location of the tumor. As you can see, some are along the spine. Brain tumors: loss of balance, headaches, and also you can get meningiomas and even mixed tumors, with the average life expectancy, 40 years.

Next one.

And what we wanted to do was just evaluate the patients neurologically to see that there wasn't any change in the status that could be attributed to the ABI and not to the disease. It's not easy to do, but I think in general we were able to accomplish that.

I felt there were eight parameters that should be evaluated to really ascertain whether or not the implant itself was responsible for neurologic deterioration.

Next slide.

And these were obviously the cerebellar function. It's right near the cerebellum, sensory function, descending and ascending tracts from the cerebrum; extraocular motion; symmetry of palate; ninth and tenth nerves; swallowing; sternocleidomastoid; all of these are nine, ten, and 11, which are near there, and just as a general check, see if there's any disparity in the reflexes and the intraocular pressure, i.e., is there any increased intracranial pressure from whatever cause.

In the 80 cases that were evaluated, we found no ABI that we could feel for sure were related to the ABI.

Next slide.

Eighty of the 90. There were no changes vis-a-vis the parameters I just went over for this.

Do you have that slide on the -- yeah, let

me just show you.

Let me just show you a little bit about -- go ahead. Oh, press the button? This is what the tumors look like, and as you can see, after you take the tumor out, there's a tremendous amount of distortion of the brain, and this is why we probably -- there may be intrinsic deficit in the nucleus itself, which it's amazing that it works as well as it does.

Next slide.

Now, this is just a post-op to show you what the ABI looks like on a scan done post-op. We can ascertain exactly where it is. We look at all of these patients to make sure that it's where we said it is.

Next slide.

And that's another one just to show the same thing.

That's really all I have to say. Thank you very much.

MS. EBINGER: Good morning. I'm Kiara Ebinger. I'm Senior Clinical Study Specialist with

Cochlear Corporation.

The effectiveness of the nucleus auditory brain stem implant system in adults and young adults with NF2 is supported by results from 60 ABI recipients in the United States and 27 in Europe. Each of these 87 individuals either have suffered or will suffer complete bilateral deafness as a result of acoustic tumor removal.

Participants in this investigation were individuals 12 years of age or older who were diagnosed with NF2. There were no preoperative audiological criteria due to the life threatening nature of CPA tumors and the elimination of residual hearing by the tumor removal surgery.

Subjects were implanted with the ABI during the first or second side tumor removal surgery, and previous gamma knife therapy in the vicinity of the cochlear nucleus was a contraindication to participation in this trial.

Next slide, please.

During this investigation 92 subjects were implanted with the ABI. Unfortunately two of those

subjects died from causes unrelated to the ABI prior to device activation, leaving a safety sample of 90 subjects.

Of those 90, 30 were not included in the effectiveness sample for the following reasons. Thirteen individuals did not receive auditory precepts at initial device activation. Ten subjects were unable to attend the three or six month evaluation usually due to health concerns or additional surgical procedures. Six subjects had been recently implanted and had not yet reached the three month evaluation, and one subject was explanted prior to his three month evaluation.

Sixty stimulable subjects with a minimum of three months of device experience and whose data were reported to us by February 9th, 1999, were submitted in support of device effectiveness.

Next slide.

A few biographic characteristics of the sample are shown on this slide. On average, participants were implanted at about 33 years of age, and one-third of them were implanted at the time of

first side tumor removal surgery, and about two-thirds of the group was female.

Next slide, please.

The study design and investigational protocol are reviewed briefly here. As I mentioned, there were no preoperative audiological criteria for the trial. Comprehensive neurological and audiological evaluations were conducted at initial device activation, three, six, nine, and 12 months after activation, and annually thereafter.

An extensive battery of recorded dependent measures was used to assess a variety of auditory skills, and patient questionnaires were also used to assess patient satisfaction and perceived benefit from the device.

Major findings from the trial are summarized in the next few slides. Due to the fact that patients with acoustic tumors have usable hearing preoperatively, device effectiveness couldn't be evaluated by comparing pre to post-op performance.

Instead, device effectiveness was evaluated using the binomial statistic to compare each

subject's performance to chance performance on each of a variety of speech perception tests.

Measures of lip reading enhancement also were used to assess device effectiveness. To quantify the improvement in speech perception when auditory cues provided by the ABI were used in conjunction with visual cues obtained from lip reading, the binomial statistic was used to compare performance in those two conditions.

The six month test interval was chosen as the submission interval in support of device effectiveness because it represented a considerable amount of device use. As described previously, patients with NF2 often have many health problems and sometimes were unable to attend follow-up appointments. So if six month data were not available for a given subject, three month data were substituted. This was felt to be a conservative treatment since it represented less experience with the device as opposed to more experience with the device.

Although all 60 subjects were evaluated on

every measure -- sorry -- at three or six month intervals, a few were not evaluated on every test. So the number of patients tested varied slightly from 60.

Next slide.

Auditory performance was assessed using a variety of recorded tests administered without visual cues. Chance performance levels for each test are indicated by the dotted lines on this slide.

The sound effects recognition test, or SERT, is a closed set measure of an individual's ability to identify common environmental sounds. This test reflects an individual's connection to and awareness of the auditory world around him. Chance performance for the SERT is 25 percent.

As shown here, the group mean was well above chance, at 54 percent correct, with individual scores ranging from 13 to 83 percent. Eighty-two percent of the subjects scored significantly above chance, indicating that the ABI facilitates an important connection between ABI recipients and the world around them.

The MTS, or monosyllable trochee spondee

test is a closed set measure of word identification that also can be scored to reflect correct identification of the stress pattern of a test item. Chance performance for stress pattern scoring is 33 percent. Mean performance for this group of ABI recipients was well above chance at 75 percent correct, with scores ranging from 21 to 100 percent. Eighty-eight percent of the subjects scored above chance on this measure.

The investigational protocol also included two closed set measures of word identification, the MTS-Word and NU-CHIPS tests. On the MTS-Word test, 80 percent of recipients scored significantly above the 8.3 percent chance level, with a group mean of 35 percent correct. MTS-Word scores ranged from eight to 88 percent correct for individuals.

For the NU-CHIPS words, chance performance is 25 percent correct, and the mean NU-CHIPS score for this group was 43 percent, with 67 percent of the sample scoring significantly above chance. NU-CHIPS scores ranged from four to 78 percent for each individual.

Performance across these two measures of word recognition are consistent and demonstrate that ABI recipients are able to possess word identification skills.

CID sentences were administered to assess subject's open sentence recognition using sound alone. This is obviously an extremely challenging task for ABI recipients, and in general subjects didn't perform as well on this measure, with a mean score of four percent correct.

Next slide.

Individual results for CID sentences, sound alone, are shown here. As you can see, many subjects did score zero on this test. However, scores ranged as high as 58 percent correct. Nine subjects scored significantly above chance, and two subjects scored over 50 percent correct.

Overall, these results are encouraging and are consistent with those previously reported for single channel Cochlear implant recipients.

Next slide.

Results of lip reading enhancement are

displayed here. Normal hearing individuals commonly integrate visual cues with auditory cues in order to understand a message, and obviously hearing impaired individuals do the same, relying even more heavily on visual cues.

For this reason, measures of the benefit received from assimilating auditory cues with visual cues are a very accurate indicator of everyday functioning for a hearing impaired individual.

Three speech perception tests were administered in multiple conditions, sound alone, vision alone, and sound plus vision. The three measures used to evaluate lip reading were the Iowa medial vowel and consonant tests and the CUNY sentences test, all of which are shown here.

For all three of these measures, sound alone performance is represented by the gold bars, vision alone by the bluish bars, and sound plus vision by the lavender bars.

Lip reading enhancement is defined as the improvement of scores when performance using the ABI sound with lip reading or sound plus vision was

compared to performance using lip reading cues alone or vision alone.

On this slide that's represented by the improvements seen between the blue bars and the lavender bars.

Overall scores for the Iowa medial vowels were higher than those for the consonants, probably because vowels are easier to hear and to lip read. Using sound alone, mean score for the vowels test was 25 percent correct. Using vision alone, the mean improved to 65 percent, and when sound was used in conjunction with vision, the mean score further improved to 71 percent, with individual scores ranging from 19 to 96 percent correct.

Fifty-five out of the 57 subjects scored significantly above chance when using the ABI with lip reading.

Because vowels are relatively easy to lip read and many of these subjects lip read very well, it's not surprising that just 11 percent of the subjects demonstrated statistically significant improvements with lip reading since the vision alone

scores were very good.

For the medial consonant test, the middle three bars on this chart, the mean score in the sound alone condition was 19 percent. Mean performance improved to 38 percent using vision alone and to 52 percent when visual and auditory cues were combined. Sound plus vision scores ranged from 30 to 85 percent correct. One-third of the group showed statistically significant enhancements in lip reading when using the ABI for this test.

Fifty-eight subjects were tested with the CUNY sentences using sound alone, the mean CUNY sentence score was four percent and ranged from zero to 57 percent correct. Using lip reading alone, the mean increased to 31 percent, and when sound and lip reading were used together, the performance mean further improved to 54 percent, ranging in individuals from seven to 96 percent correct.

Next slide.

Individual results for the CUNY sentences are shown here. Vision alone scores are represented by the lavender portion of each bar, and sound plus

vision is represented by the maroon portion of each bar.

You can see just by the amount of maroon on this slide that the ABI does provide a good deal of benefit to these patients. Specifically, using the ABI in conjunction with lip reading, 85 percent of subjects improved significantly over their lip reading alone scores.

In addition, when using both sound and vision, every subject scored significantly above chance. These results are very exciting since the understanding of sentences when using both sound and vision is a fundamental component of everyday communication.

Next slide.

This slide summarizes results for CUNY sentence scores over several years of device use. Again, vision alone scores are represented by lavender and sound plus vision by maroon. As you can see, although subject numbers do decrease over time, performance does remain very stable.

Notice that the vision alone scores or the

lavender portion stays essentially the same, while the auditory component of performance appears to improve slightly over time. Without the ABI, this group of ABI patients' communicative abilities would be reflected just by the lavender portion of those bars.

Next slide.

As additional support for the efficacy of the ABI system, European clinical trial results were included in our PMA application and are summarized very briefly here. Seventeen clinical trial patients were implanted with the nucleus 22 21-electrode device. Data are included for another ten pilot subjects who are implanted with devices that differed only very slightly from the clinical trial device.

Demographic characteristics of this group were very similar to what we saw in the U.S. trial, with the exception that there were more males in the European group.

Statistical grouping of this data was precluded by the fact that testing was conducted in six different languages and using different methods and materials.

Next slide.

Overall, the results of the European trial were very consistent with the findings of the U.S. trial. As shown here, the ABI provided most recipients with the ability to recognize environmental sounds, identify words in a closed set, achieve open set sentence understanding in a few cases, and enhance lip reading with auditory cues.

Next, please.

I think we can all grasp these performance results from an intellectual perspective, but most of us really can't conceive how these functional gains really impact the quality of life for individuals with NF2. So in an effort to better understand these results from the patient's perspective, the investigational protocol also included patient questionnaires.

Next slide.

Performance questionnaire was administered to patients at each evaluation beginning at three months. This questionnaire assessed issues of daily device use and perceived helpfulness in a variety of

listening situations.

The next couple of slides summarize some of the more salient questionnaire items. Data are shown for 51 of the 60 subjects who completed the questionnaire at either their three or six month eval.

Next slide.

When asked about daily device use, respondents reported using the speech processor between zero and 17 hours per day, with a mean for all subjects of just over seven hours a day. Eighty percent of the subjects who reported little or no daily use were first side subjects with usable hearing in the other ear.

Subjects who were implanted at the time of second side tumor removal reported using the device for an average of about ten hours per day.

Next slide.

Subjects were asked to rate the helpfulness of the ABI in a variety of specific listening situations using a six point rating scale, where a rating of one indicated no help at all, and a rating of six indicated very helpful.

Overall subjects rated the ABI most helpful in situations where auditory input could be supplemented with visual cues. These situations, including lip reading in a one-on-one situation, listening to a familiar voice with lip reading in quiet, identifying environmental sounds, and general social interaction.

Next slide.

Subjects reported that the ABI was least helpful for strictly auditory tasks where lip reading cues were not available. These situations included listening to the radio, listening to music, and listening to either an unfamiliar or a familiar voice and noise without the aid of lip reading.

In summary, results of the performance questionnaire demonstrate that recipients rated the ABI as being helpful in many social situations, particularly when the information from the ABI could be supplemented with visual cues.

Next slide.

The performance questionnaire reflected a relatively short duration of experience with the

device as patients completed it at either the three or six month evaluation. In order to better assess long term device use and patient outcomes, a final questionnaire was administered. Responses to this questionnaire reflected up to six years of device use.

Forty-four subjects returned the final questionnaire prior to closure of the databases. In general, despite fairly modest performance outcomes, such as small number of recipients with open set speech perception, patients reported enhanced quality of life and improved communicative function when using the ABI.

Next slide.

Seventy-five percent of respondents reported wearing their devices daily. The remaining 25 percent were not regular users for a variety of reasons, including implantation during first side tumor removal with usable hearing in the other ear, other acute health concerns or surgeries, and in a few cases, lack of perceived benefit.

Eighty percent of respondents reported that they received benefit from their ABI. When asked

about the decision to receive the implant, 84 percent felt that the decision to get the implant was the right one, and 73 percent reported that they would recommend an ABI to others.

These results indicate that the majority of respondents are satisfied with the ABI and with the benefits they receive.

Next slide.

In conclusion, performance results demonstrate that the ABI allow recipients to recognize environmental sounds, identify stress patterns in words, enhance their lip reading abilities, and in a few cases, achieve open set, auditory only sentence understanding.

Perhaps more importantly, results of patient questionnaires confirm that these auditory benefits can lead to significant and meaningful improvement in quality of life for these individuals.

The results of the clinical trial as reported to FDA in detail and summarized here support the effective application of the nucleus 24 ABI in individuals with NF2.

these days.

It's important, we believe, to clearly communicate the relatively high non-stimulation rate as well as other possible adverse effects.

The claims that we proposed at our speech perception claims in this section are based on the individual results for the 60 effectiveness subjects. We're also requesting permission to propose and use four claims, I believe, that are based on questionnaire data coming from the written responses of 44 subjects.

Next slide.

The areas where we're asking for claims are just Kiara has described. We believe that the benefits of the ABI pertain to the identification of environmental sounds, lip reading enhancement, open set sentence recognition, as well as self-reported benefit satisfaction and information regarding device use.

Next slide.

The identification of environmental sound claims that we've proposed are here. The first claim

is an aggregation of the single subject results basically counting up the number of subjects who demonstrated statistically significant performance improvements compared to chance using the binomial model as Martyn explained.

So 82 percent of the subjects, 49 of 60, scored significantly above chance, which was 43 percent, on a recorded closed set test of environmental sound identification. So most of the sample is experiencing benefit, statistically significant benefit in this area.

The second claim attempts to attach to that some magnitude of the effect. So using the ABI, subjects recognized 54 percent of common environmental sounds on average and 65 percent of the sample, 39 of 60 subjects, recognized 50 percent or more of the sounds. So not only do we want to tell patients that they're very likely to improve; we want to give them some kind of an index as to how much improvement to expect.

Next slide.

This is the same sort of format for the

lip reading enhancement claims. Eighty-five percent of the tested subjects, 49 of 58, demonstrated statistically significant improvements in open set sentence understanding when using the ABI in conjunction with lip reading.

Secondly, the average sentence recognition score improved from 31 percent for lip reading alone to 54 percent when subjects combined auditory information from the ABI with lip reading.

Next slide.

This final claim concerns open set sentence recognition. It is quite modest. Using sound alone, just 12 percent of study participants scored greater than ten percent on a difficult open set test of sentence understanding.

We believe that a claim like this is important, again, in order to give ABI patients some context, something to which they can compare the results that they're likely to hear about Cochlear implant patients.

Next slide.

These are our questionnaire based claims.

Firstly, 61 percent of subjects, nine of 31, who received the device following removal of a second side tumor reported using the ABI on a daily basis for ten or more hours.

Eighty percent, 35 of 40 of the respondents reported receiving benefit from the ABI, and 84 percent, 37 of 44, indicated that the decision to receive the ABI was the right one, and lastly, 73 percent, 32 of 44, of the respondents would recommend an ABI to others.

Next slide.

The last section of the insert that I'd like to discuss pertains to training requirements. As Dr. Brackmann and Dr. Hitselberger described earlier, this isn't an easy surgical procedure. We believe that physicians should be quite experienced in both tumor removal procedures and Cochlear implant surgery.

Obviously they should be thoroughly familiar with the anatomy of the fourth ventricle and the ABI surgical procedure itself.

We strongly believe that the ABI project is a team project, and that the implanting surgeon

work with an experienced team of professionals. These professionals should include a neurosurgeon, a neurologist, an audiologist, and lastly, an electrophysiologist.

Next slide.

The implanting physician and ABI team will be asked to attend a manufacturer sponsored training program, and then secondly, to kind of further the training program that they attend, we will be asking that the newly implanting ABI surgeon invite a designated consultant, someone identified by us to be present and support his or first ABI surgery.

Next slide.

Lastly, with respect to post market surveillance, PMS programs, as you know, are intended to address long term questions regarding the safety and effectiveness of a device. We don't believe that PMS is indicated for the ABI system at this time.

The safety issues, we believe, are very well characterized in the current sample. As you know, there is a relatively high rate of non-stimulations. However, the other complications are

generally minor and are characteristic of Cochlear implant surgery.

The longitudinal data that Kiara summarized that is reported in quite more detail in our submission to FDA clearly supports the stability of the effectiveness outcomes over time. I'd just like to remind you that this IDE has been open since 1994. Some of these patients have been implanted six, seven years. They've contributed a lot to this investigation and, to be honest, they're kind of tired of coming.

The sample includes over 200 person-years of experience, which again we believe will represent the longitudinal effects of this device.

That concludes our presentation. We'll be very happy to entertain your questions.

CHAIRMAN PATOW: Thank you very much.

I'd like to thank the presenters for their very clear and organized presentations.

We now have some time for panel questions. Dr. Hood?

DR. HOOD: I had just a couple of

questions relative to the insert and the numbers. I'm unclear about the environmental sounds.

CHAIRMAN PATOW: That would be a great idea. If we could have the presenters come up to the table where the microphones are, that would save some time.

DR. HOOD: From the data presented, I understand that the environmental sounds has a chance level of 25 percent, and in the labeling it talks about subjects scoring significantly above chance of 43 percent. I'm wondering if it's a different measure that has a different chance level that's being used for this claim.

MS. ARNDT: I'm so sorry, Linda. I didn't quite hear the first part of the question.

DR. HOOD: Okay.

MS. ARNDT: Could you tell me one more time?

DR. HOOD: It has to do with the environmental sounds and the therapeutic claim that talks about a chance score of 43 percent. In the data that we were presented relative to the SERT, the

environmental sounds has a chance level of 25 percent.

MS. ARNDT: Right.

DR. HOOD: I'm wondering if there are different measures contributing to this.

MS. ARNDT: No, I think you've identified an error. Chance performance on the SERT is 25 percent.

DR. HOOD: Okay.

MS. ARNDT: So the results actually looked better than we claimed.

DR. HOOD: Okay, and just one other minor point along that line. On the questionnaire results, you mentioned 61 percent of the subjects, but nine of 31, and I wondered if that's just another calculation?

MS. ARNDT: No, there we're very specifically talking about device use in patients who received -- I'm sorry, Linda. Tell me one more time. I should have brought my presentation up.

DR. HOOD: Okay.

MS. ARNDT: You're referring to the?

DR. HOOD: The questionnaire results with an n of 44 subjects.

MS. ARNDT: Yes.

DR. HOOD: And you're talking about the fact that 61 percent of the subjects receiving the device following removal of a second side tumor report using it on a daily basis for ten or more hours, and the number that you have describing the subjects that contributed to that I think is just another dropped number.

MS. ARNDT: It actually isn't. This denominator is an n of 44. We had 44 recipients who sent us back their questionnaires. Of these 44, 31 received the device following the removal or at the time of the removal of their second neuroma. The remaining patients received the device at the removal of their first side tumor, which means they still had normal or near normal hearing in the contralateral ear.

So we were trying to describe device use in the population of patients who replied on this questionnaire for whom you would expect them to use the device. They are profoundly deaf.

Does that make sense?

We've addressed the other issue in another section of the package insert called the clinical considerations, and there we have described to potential recipients that if they do receive an ABI at the time that their first tumor is removed, because their hearing is likely to be normal, that they're not likely to use it very much until the time that the second tumor is removed.

DR. HOOD: Okay.

DR. BRACKMANN: But it is 31 of 44, which is 66, not nine of 31.

MS. ARNDT: Oh, I see. Well, if we have an error, we'll correct that.

DR. HOOD: Okay.

MS. ARNDT: Long road to a little house.

DR. HOOD: Could I ask one other question?

CHAIRMAN PATOW: Yes.

DR. HOOD: This is relative to the magnet, and am I clear that magnets are not used with this, that the internal device -- that none of the patients have the magnet on the internal device?

DR. BRACKMANN: That is correct. You have

the option. It's a removable magnet.

We do have a subset of patients who have only bilateral acoustic tumors. There are families in which the phenotype only produces bilateral acoustic tumors so that you would have the option perhaps when both tumors are removed of leaving the magnet in place, but we have not done that.

We recommend removal of the magnet in all cases. None of the device is, therefore, ferromagnetic, and so it is MRI compatible with removal of the magnet.

DR. HOOD: Okay, and I also just wanted to be clear that the 60 patients that were entered into the effectiveness data all are using the adhesive method of connection rather than the magnetic.

MS. ARNDT: That's right.

DR. HOOD: Thank you.

CHAIRMAN PATOW: Other questions? Dr. Woodson.

DR. WOODSON: Yes. This is Dr. Woodson.

Dr. Brackmann, you mentioned that in most of the cases of the non-stimulation it was probably

due to cochlear nucleus distortion, which makes me wonder if there were other factors, and I'm wondering could you tell at the time of surgery that they were not going to stimulate? Is there any factor that you could identify maybe on the pre-op scans or any way of identifying prior to putting an implant in that it's going to be futile for a particular patient?

DR. BRACKMANN: Of the 14 non-stems, there were seven in which an electrically about the EABR could not be elicited intraoperatively. So that would have predicted that they would have been non-stimulators.

On the other hand, we have two or three that had no intraoperative EABRs who were very good performers. So we have felt insecure in not offering it to patients despite the fact that the EABR is not obtainable.

In the other seven where EABRs were obtained intraoperatively, we have to believe that it was device migration. In a couple of those cases, we've identified a very patchless, large, lateral recess of the fourth ventricle which did not hold the